genetic disease regardless whether the patient asks for such advice. Referrals to genetic counseling clinics may be indicated if the problem is complex. Genetic counseling requires knowledge regarding the nature and natural history of the disease. Often, similar appearing diseases may not be genetic at all or may be inherited by different mechanisms. The usual approaches to diagnosis such as careful history and physical examination in addition to full exploration of the manifestations of the disease in affected relatives together with laboratory and radiologic examinations will be necessary in the workup. There are no special genetic tests available in most instances. The good genetic counselor provides full understanding of the risks and burden of the disease to the family and explains all the reproductive options available. The final decision regarding future reproduction is made by the family involved. Most genetic counseling is done by medical geneticists in university and hospital centers. Nonmedical professionals trained in certain aspects of human genetics and counseling are increasingly working with MD geneticists and will have an important role to play in this field since not enough trained medical geneticists are available. Considerably more experimentation and trials of different organizations and modes of counseling will be required to elaborate an ideal scheme for genetic counseling. The satellite or outreach program which was worked out by the medical genetics unit at the University of California and which covers several areas of California is an interesting experiment of this sort.

As modern parents want their few children to be as healthy as possible, demands for genetic counseling will increase. All physicians therefore need to be conversant with the principles and recent advances in medical genetics.

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The Thalassemia Syndromes

DAVID WEATHERALL is the guru of that band of international thalassemologists who gather from time to time to ponder the many tantalizing aspects of this fascinating inherited disease. As Weatherall points out, the thalassemia syndromes are not at all rare. In fact, they constitute an international public health problem of staggering proportions. As many as 30 percent of the inhabitants of Cyprus are thought to be carriers of beta$^+$-thalassemia. Hence, it is estimated that 3 percent of all newborns on that island may be homozygotes. When one considers the treatment required to maintain life in such patients, the implications boggle the imagination of organizers of delivery of primary care.

Weatherall has ably reviewed the molecular genetics of thalassemia in his scholarly Paul Aggeler Lecture, which appears elsewhere in this issue, and has touched on the important clinical aspects as well. He emphasizes how the unbalanced globin chain synthesis in thalassemia creates a condition in which the total hemoglobin in the red cell is reduced. But, unlike the relatively simple hypochromic cell of iron deficiency, the thalassemia cell is further encumbered by accumulation of the unaffected globin chains produced in relative excess. These precipitate, damage the cell and thereby cause the massive ineffective erythropoiesis that creates the proliferative and hypermetabolic consequences of the disease. These useless red cells proliferate throughout the marrow, liver and spleen and even spread out from the vertebrae into the thoracic and abdominal gutters. The children die with terminal cachexia like patients ravaged with cancer. Indeed, the disease is often superficially indistinguishable from a chronic malignancy.

There is no need in this editorial to comment further on Weatherall's masterful review of the molecular biology, except to reemphasize how magnificently the data presented illustrate the vital interaction between the basic sciences and clinical medicine. Those who argue about the relevance of basic science should read and reread this fascinating story.

In the conclusion of his review, Weatherall proposes that the long-term hope for treatment of patients with thalassemia lies in "gene manipulation" as "the only feasible approach." This may

be true, but the way is fraught with very serious difficulties. In the vast majority of patients with beta thalassemia, the β gene is present but poorly transcribed. Hence, it might be possible to coax the errant gene into the production of messenger ribonucleic acid (RNA). But the mutation may make it impossible for any stimulation of transcription to be affected. Perhaps more likely is the possibility that the normal gamma genes may be stimulated to increase their rates of production. Finally, there are those who hope that normal globin genes wrapped up in plasmids might serve a therapeutic purpose. These are all approaches that are feasible and challenging, and as methods of growing erythroblasts *in vitro* become more practical, *in vitro* models of such systems will become testable at the bench. Their translation to the bedside will obviously take far longer.

In the meanwhile, constant reassessment of therapeutic approaches now at hand must be continued. Prevention through prenatal diagnosis is in fact a reality. Far more work is needed to render this procedure freer of obstetric hazards and more reliable biochemically. But there have been at least 30 such attempts carried out in London, New Haven, Boston and San Francisco, and most have been successful. Much of the impetus for this work comes from the laboratory of Dr. Y. W. Kan in San Francisco.

But, what can be done for the patients now at hand? Bone marrow transplantation is a logical thought, and the technical aspects are increasingly understood due in large part to the efforts of Drs. E. D. Thomas and Reiner Storb and their co-workers in Seattle. However, a decision to carry out a bone marrow transplantation in a very young patient with thalassemia would be extraordinarily difficult in view of the fact that conservative management should offer an 18 to 20 year life span for the patient as opposed to the 40 to 50 percent risk of immediate mortality due to the transplant procedure. Obviously, if one elects to do a marrow transplantation late in the course of life span of a patient with thalassemia, sensitization by transplantation antigens present in transfused blood will most assuredly compromise any hopes for success. Furthermore, the liver disease secondary to iron overload would notably increase the hazard of immunosuppressive therapy, particularly with cyclophosphamide. Transplantation certainly presents no easy solution at this time.

Only recently have investigators of the clinical aspects of the thalassemia problem begun to reexamine the basic precepts of care of these patients. Stimulated by the aggressive management techniques of Bernadette Modell, Elizabeth Letzky and their colleagues in London, a more quantitative examination of the problem of transfusion and elimination of iron overload has begun to emerge. Up to this time, it has been generally accepted that the most efficacious method of treatment of a patient with thalassemia is the elevation of the circulating hemoglobin concentration to at least 10 grams per 100 ml by transfusion. This accomplishes two purposes: the patient is afforded a higher oxygen carrying capacity and, more important, the massive proliferation of tne red cell mass is considerably reduced by this manipulation of the erythropoietin response. But the long-term consequences of this physiologic approach are disastrous because the iron overload induced by the red cell transfusions eventually results in intractable cardiac failure or arrhythmia.

Two approaches to the problem of hemosiderosis must be considered. First, and most obvious, is the development of effective chelation programs. Until very recently, the most promising drug, desferrioxamine, has been considered to be of little value because a single intramuscular dose of the drug induces only a small iron excretion. But recent studies have shown that prolonged administration of a standard dose of desferrioxamine may in fact induce very large rates of iron excretion. In recent studies carried out at the Children's Hospital Medical Center and the National Institutes of Health, as much as 80 mg of iron have been eliminated per day from such patients by the use of chronic subcutaneous administration of this drug. The desferrioxamine is delivered to the subcutaneous tissues of the anterior abdominal wall by means of portable infusion pumps which infuse a small but constant dose of the drug into the tissues at a constant rate.

Another approach follows a critical review of the problem of excess erythroid cell proliferation. We use transfused red cells to suppress marrow erythropoiesis in thalassemia, but it is entirely possible that certain chemotherapeutic agents might accomplish this necessary reduction of erythroid proliferation and would thereby enable the clinician to deliver less red cells to the patient. After all, the number of red cells required to provide sufficient oxygen carrying capacity for

a reasonably normal life is considerably less than that required to elevate the total hemoglobin concentration to 10 grams per 100 ml or more. Many patients with chronic anemia who are not encumbered by ineffective erythropoiesis exist very comfortably at hemoglobin concentrations of 6 to 8 grams per 100 ml. Whether the use of chemotherapeutic agents to reduce red cell proliferation would create unacceptable side effects is not known, and animal studies will be required fully to evaluate this type of approach.

At least as a result of continuous thinking about the thalassemia problem, novel approaches to therapy and prevention are in fact proceeding pari passu with the great advances in molecular biology reviewed here by Dr. Weatherall. As is true of all clinical approaches to difficult inherited disease, progress is slow. But it appears to be steady and occurring on several fronts. It seems likely that on the delightful occasion of Dr. Weatherall's next visit to San Francisco, even more advances in the molecular biology and treatment and prevention of thalassemia will be reported. Certainly many of these advances will be made by Western medicine.

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A New Challenge for Continuing Medical Education

RECENT LEGISLATION in a growing number of states seeks to link continuing medical education with evidence of continuing professional competence of a practicing physician. This is a most reasonable approach, but it poses a real challenge for both a practicing physician who must find the continuing education he may need to assure his own continuing competence, and for those who must provide the kinds of continuing education practicing physicians will need to remain competent in many specialties and in diverse settings.

There is a clear need for a more precise identification of just what it is that makes a physician competent—or not competent. There is obviously more to it than simply that he continues through a lifetime of practice the same kind of education that sufficed for graduation from medical school, for specialty certification or for licensure. For one thing, the requirements for these are generally considerably less differentiated than what may be needed for competence in a specific practice situation, and the busy practitioner has little time to waste learning things that he does not need to know. On the other hand, there are other kinds of things he should know to be competent in his own practice that were not taught in medical school. For example he should be aware not only of the drugs and technical procedures that might help a patient, but of the community resources that are available and how to use them.

A new challenge to continuing medical education would now appear to be to address the problem of just what is involved in the professional competence of a practicing physician in his own practice situation, and to set about making available continuing education that will enable every practitioner to assure his continuing professional competence in his own practice situation.

—MSMW